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Pathology RS

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FIBROSING DISEASES

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FIBROSING DISEASES

One of the major categories of chronic interstitial lung diseases

- **Idiopathic Pulmonary Fibrosis**
- **Nonspecific Interstitial Pneumonia**
- **Cryptogenic Organizing Pneumonia**
- **Pneumoconioses**

IDIOPATHIC PULMONARY FIBROSIS

- Pulmonary disorder of **unknown etiology** that is characterized by **patchy, progressive bilateral interstitial fibrosis**.

- **cryptogenic Fibrosing alveolitis**.

Other name Because of its unknown etiology

- The radiologic and histologic pattern of fibrosis is referred to as **Usual interstitial pneumonia (UIP)** pattern.

- **Males , Never before 50s**

IDIOPATHIC PULMONARY FIBROSIS

- **Diagnosis:**
  - **radiologic and histologic** pattern are needed
  - Diagnosis **of exclusion**

The histologic findings in the lung are not specific and may be present in other entities such as asbestosis and collagen vascular diseases so diagnosed by exclusion

PATHOGENESIS

This interstitial fibrosis is believed to result from:

- Repeated cycles of epithelial activation/injury by some unidentified agent
- Defective repair of alveolar epithelium
- Genetic predisposition

GENETIC FACTORS:

- Germ line mutations leading to **loss of telomerase** associated with increased risk.
- **cellular aging** since IPF is a disorder **of older adults**.
- 35% have a genetic variant in the ***MUC5B*** **gene** that alters the production of mucin
- Smaller number have germ line mutations in **surfactant genes**.

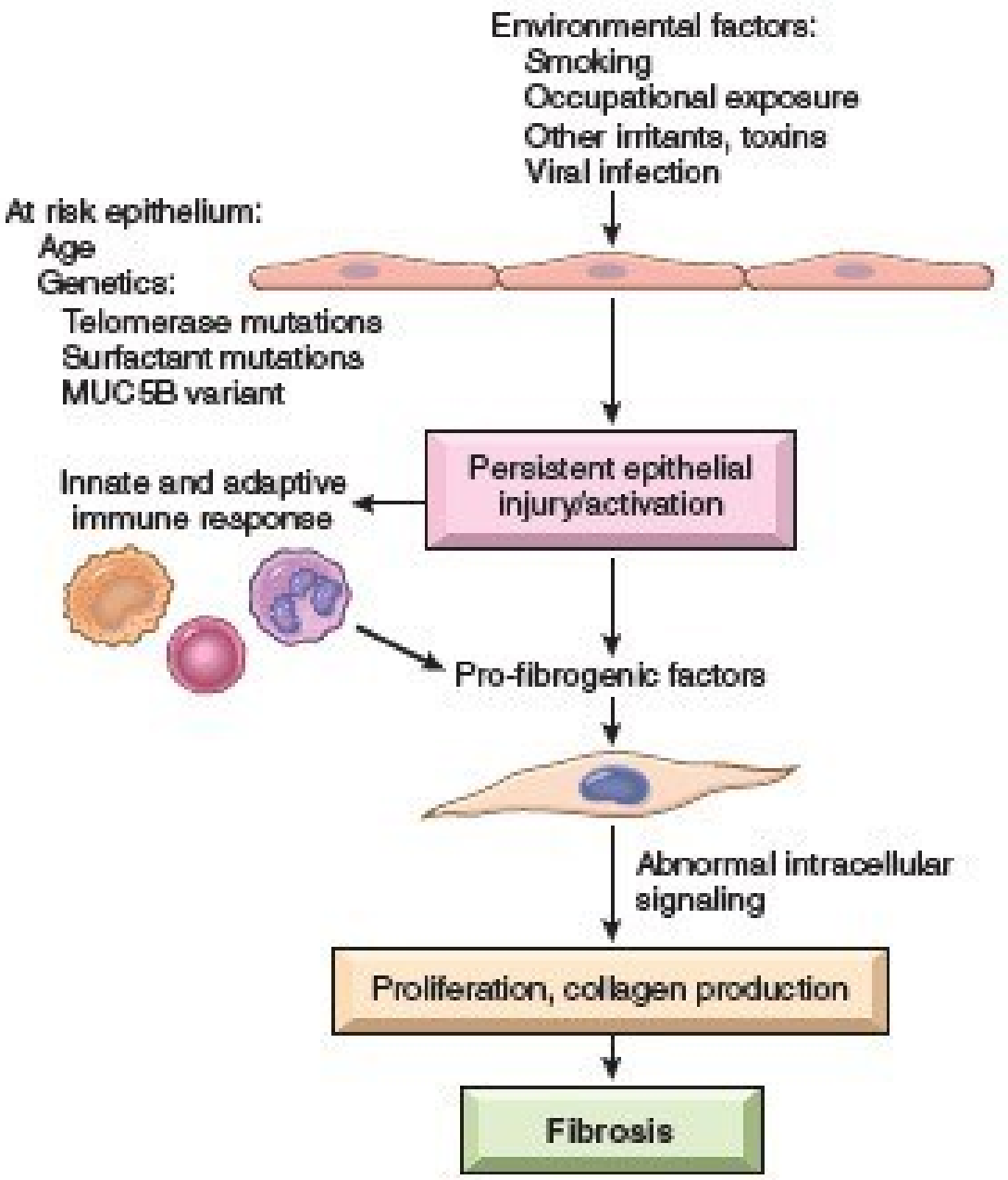

Fig. 13.13 Proposed pathogenic mechanisms in idiopathic pulmonary fibrosis. See text for details.

This figure shows the proposed pathogenic mechanism in idiopathic pulmonary fibrosis
The exposure of the epithelium at risk (due to cellular aging & genetic factors) to certain environmental factors such as smoking , occupational exposure , other irritants and viral infections will result in persistent epithelial injury and activation. This persistent injury in the presence of abnormal epithelial repair at the site of the chronic injury and inflammation will result in exuberant fibroblastic or myofibrobalstic proliferation mediated mainly by the pro-fibrogenic factors, transforming growth factor beta

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MORPHOLOGY, MACROSCOPIC:

- **Cobblestones appearance** of the pleural surface, due to retraction of scars along the interlobular septa.

https://en.wikipedia.org/wiki/Cobblestone


Cobblestones appearance of the pleural surface

- The cut surface shows fibrosis (**firm, rubbery white areas**)
- **Lower lobe and subpleural regions** and along the **interlobular septa** are mostly affected.
- **Usual interstitial pneumonia (UIP) pattern of fibrosis**

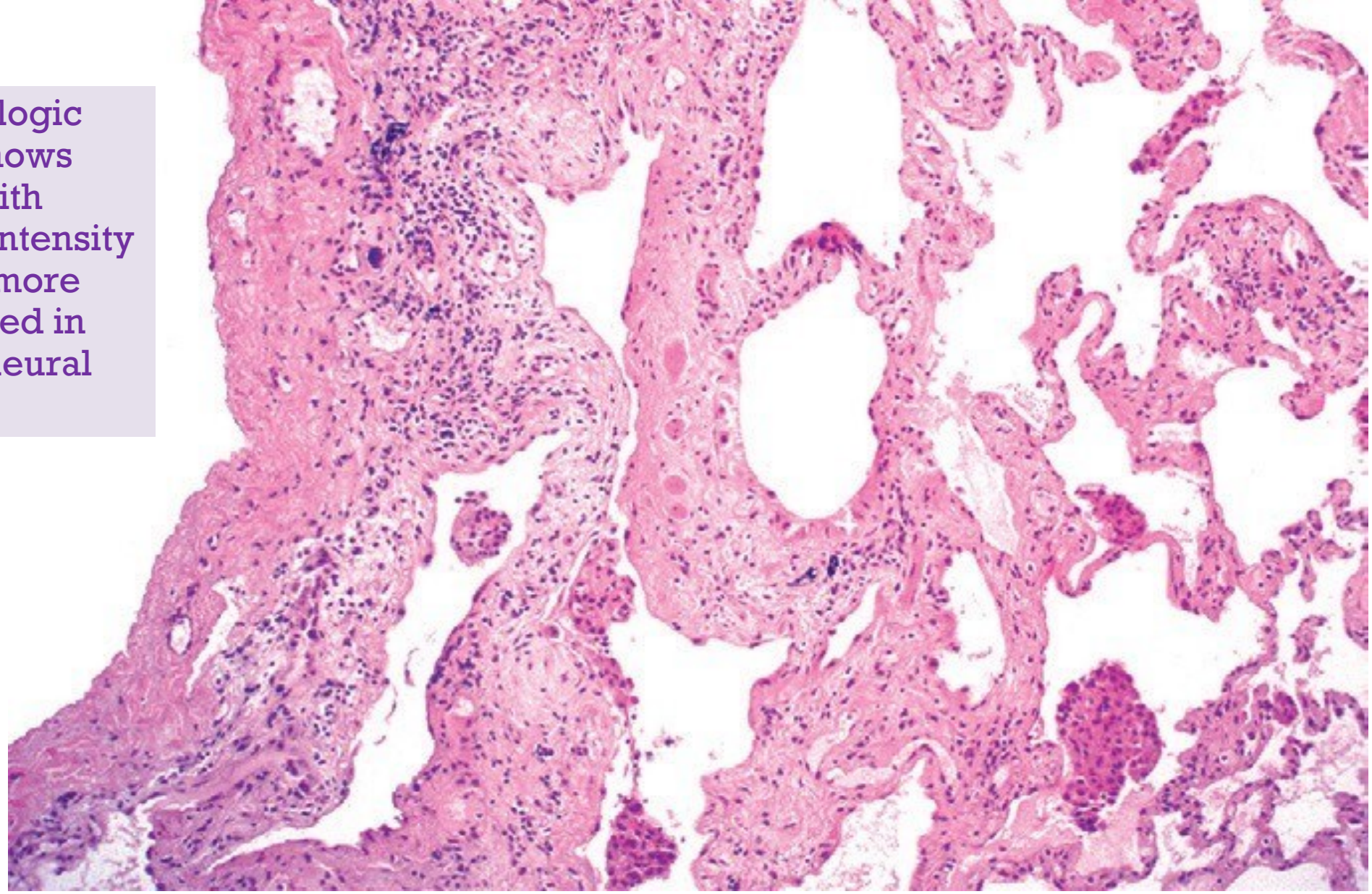
MORPHOLOGY, MICROSCOPIC:

- Hallmark is **patchy** interstitial fibrosis (consisting on an alveolar septal infiltrate of mostly lymphocytes with occasionally plasma cells , mast cells & eosinophils), **which varies in intensity and worsens with time**.

- **Temporal heterogeneity is typical** (**early and late lesions coexist**):
  - Fibroblastic foci are fibroblastic proliferations and considered the earliest lesions.
  - Late lesions are more collagenous and less cellular and may show honeycomb fibrosis

Is a result of dense fibrosis that causes collapse of alveolar walls and the formation of cystic spaces which is lined by hyperplastic type 2 pneumocytes or bronchiolar epithelium

This histologic section shows fibrosis with variable intensity as being more pronounced in the sub pleural region



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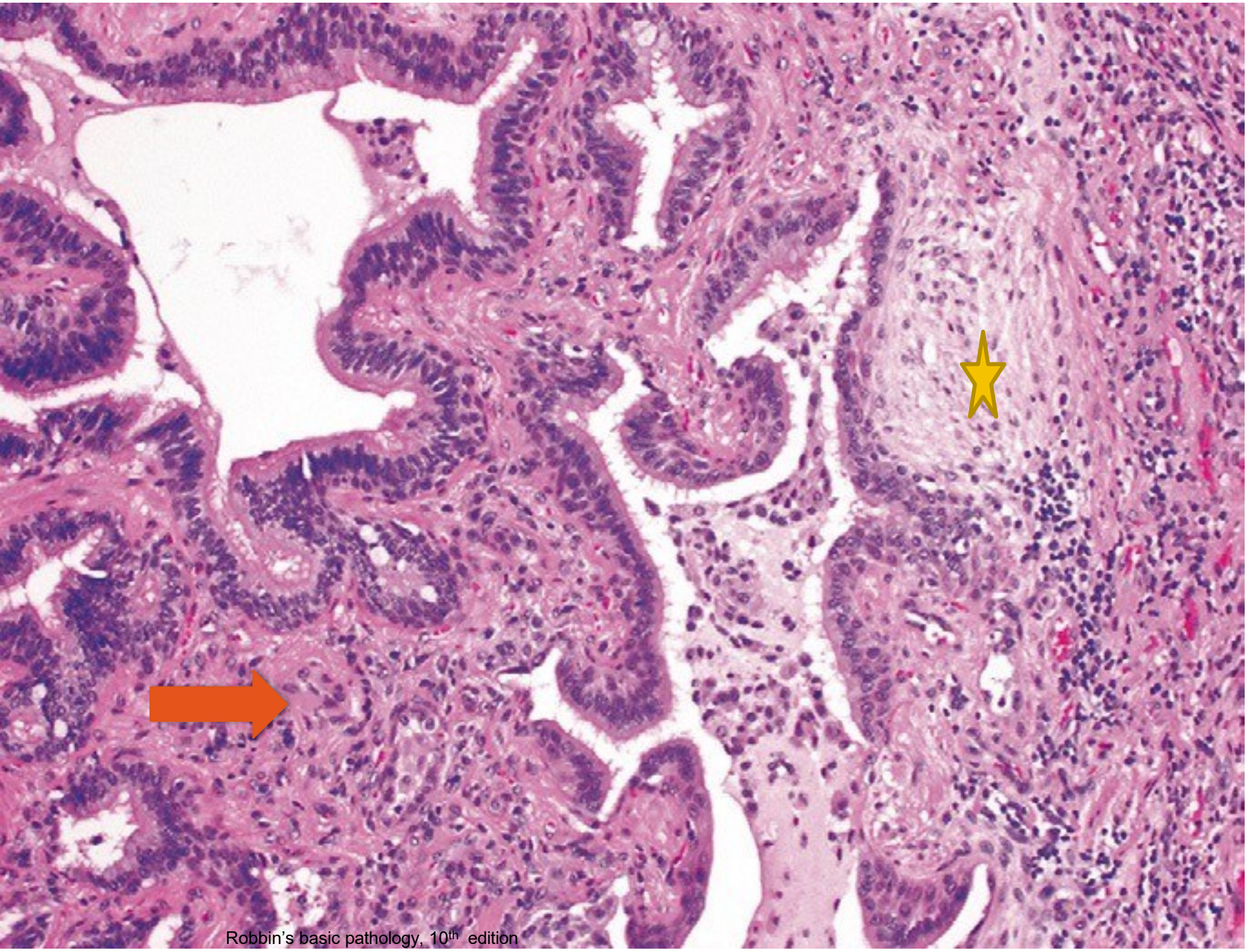

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This histologic section shows a case of usual interstitial pneumonia
The yellow star shows : fibroblastic focus with fibers running parallel to the surface and bluish myxoid extra cellular matrix

Honeycomb is present to the left and in advanced cases you may see secondary secondary pulmonary hypertensive changes such as intimal fibrosis and medial thickening of the pulmonary arteries

CLINICAL FEATURES

- **Gradual onset of Nonproductive cough** and **progressive dyspnea.**

- **On physical exam**, **“dry” or “Velcro”-**like crackles during inspiration.

- Cyanosis, cor pulmonale, and peripheral edema may develop later.

- Radiologic findings include subpleural and basilar fibrosis, reticular abnormalities, and “honeycombing”

So the combined clinical and radiologic findings are often diagnostic

OUTCOME:

- The overall prognosis remains **poor**
- survival is only **3 to 5 years**
- **lung transplantation is the only definitive treatment**.

MANAGEMENT:

- Anti-inflammatory therapies

Although they have proven to be of a little use since inflammation is of secondary pathogenic importance

- Anti-fibrotic therapies

More important and now proved to be of use in patient with idiopathic pulmonary fibrosis

FIBROSING DISEASES

- Idiopathic Pulmonary Fibrosis
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NONSPECIFIC INTERSTITIAL PNEUMONIA (NSIP)

- **Chronic bilateral interstitial lung disease of Unknown etiology**
- despite its name it has **Distinct clinical, radiologic, and histologic features.**
- **Better prognosis** than IPF.
- Dyspnea and cough of several months

NONSPECIFIC INTERSTITIAL PNEUMONIA

- **frequent association** with collagen vascular disorders such as rheumatoid arthritis.

- characterized by **patchy but uniform** mild to moderate **interstitial chronic inflammation and/or fibrosis**.

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CRYPTOGENIC ORGANIZING PNEUMONIA

The old name is bronchiolitis obliterans organizing pneumonia

- Uncommon
- Unknown etiology
- Cough and dyspnea
- CXR: subpleural or peribronchial patchy airspace consolidation.

Due to intra-alveolar plugs of loose organizing connective tissue

- Microscopically, Intraalveolar plugs of loose organizing connective tissue.

- Some patients recover spontaneously while most require treatment, usually with oral steroids.

A 59 year old lady works as electrical engineer and nonsmoker, has a 4-month history of increasing dyspnea. On examination she is afebrile and normotensive. Chest CT shows lower lobe reticular opacities. A transbronchial biopsy is performed and microscopically shows patchy interstitial inflammation with lymphocytes and plasma cells. No

organisms are identified. Her condition slowly worsens over the next 10 years. Which of the following is the most likely diagnosis?

A) Desquamative interstitial pneumonitis

B) Hypersensitivity pneumonitis

C) Idiopathic interstitial fibrosis

D) Nonatopic bronchial asthma

E) Nonspecific interstitial pneumonia

Not episodic , gradual progression

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Restrictive lung disease

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PNEUMOCONIOSES

Includes asbestosis,silicosis, coal workers pneumoconiosis

- **lung reaction to inhalation of mineral dusts, organic and inorganic particulates, chemical fume and vapor.** Considered as occupational lung disease

It can develop when air borne dusts particularly the mineral dusts are inhaled in work , the dust particles remain in the lung where they can cause inflammation, fibrosis & scarring

- The most common mineral dust are induced by inhalation of **Coal dust, silica, and asbestos**.

- usually related to **workplace exposure**, except for **Asbestos**

- In **Asbestos**:
  - The risk of cancer is increased in family members of asbestos workers and to individuals exposed outside of the workplace.

Table 13.3 Mineral Dust–Induced Lung Disease

Agent	Disease	Exposure
Coal dust	Simple coal worker's pneumoconiosis: macules and nodules Complicated coal worker's pneumoconiosis: PMF	Coal mining
Silica	Silicosis	Sandblasting, quarrying, mining, stone cutting, foundry work, ceramics
Asbestos	Asbestosis, pleural effusions, pleural plaques, or diffuse fibrosis; mesothelioma; carcinoma of the lung and larynx	Mining, milling, and fabrication of ores and materials; installation and removal of insulation

PMF, Progressive massive fibrosis.

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PATHOGENESIS:

- The reaction depends on **size, shape, solubility, and reactivity** of the particles.

Regarding solubility & reactivity

Caol dust is relatively inert so large amounts must be deposited in the lung before the lung disease is clinically detectable .silica ,asbestos & beryllium on the other hand are more reactive than col dust resulting in fibrotic reaction at lower concentrations

Regarding size

- **Particles that are 1 to 5 µm in diameter are the most dangerous**

Got lodged at the bifurcation of the distal airways

Particles greater than 5 to 10 micrometer are unlikely to reach the distal airways whereas particles smaller than 0.5 micrometer move to the alveoli and out of them , often without deposition and injury

Usually most inhaled dusts are entrapped in the mucous blanket so they are removed by ciliary movement, however some of the particles become impacted at the alveolar duct bifurcation where macrophages accumulate and engulf the entrapped particles

- **The pulmonary alveolar macrophage is a key cellular element** of lung injury and fibrosis.

After phagocytosis many particles activate the inflammasomes and induce the production of interleukin 1 and other factors which initiate an inflammatory response leading to fibroblastic proliferation and collagen deposition

- **Tobacco smoking** worsens the effects of all inhaled mineral dusts, more so with asbestos .

PNEUMOCONIOSES

- Coal Worker's Pneumoconiosis (CWP)
- Silicosis
- Asbestosis and Asbestos-Related Diseases

COAL WORKER'S PNEUMOCONIOSIS

- Spectrum of changes:
  - **Asymptomatic anthracosis**: pigment accumulates without a cellular reaction.
  - **Simple coal worker's pneumoconiosis (CWP):** accumulations of macrophages with little to no pulmonary dysfunction
  - **Complicated CWP or progressive massive fibrosis (PMF) :** extensive fibrosis and compromised lung function.
    - less than 10% of cases of simple CWP progress to PMF.

- **PMF is generic >>**
  - confluent fibrosing reaction in the lung
  - can be a complication of any one of the pneumoconioses

- Coal is mainly carbon, in addition to other inorganic minerals

& Crystalline silica

MORPHOLOGY:

- **Pulmonary Anthracosis:**
  - Seen also in **urban dwellers and tobacco smokers**.
  - Inhaled carbon pigment is **engulfed by alveolar or interstitial macrophages**
  - **accumulate in the connective tissue along the pulmonary and pleural lymphatics and in draining lymph nodes.**

Simple CWP:

- **Presence of coal macules and nodules**
  - **Coal macules :** dust-laden macrophages , small amounts of collagen fibers arrayed in a delicate network

- Upper lobes and upper zones of the lower lobes are more heavily involved.

- **centrilobular emphysema** can occur.

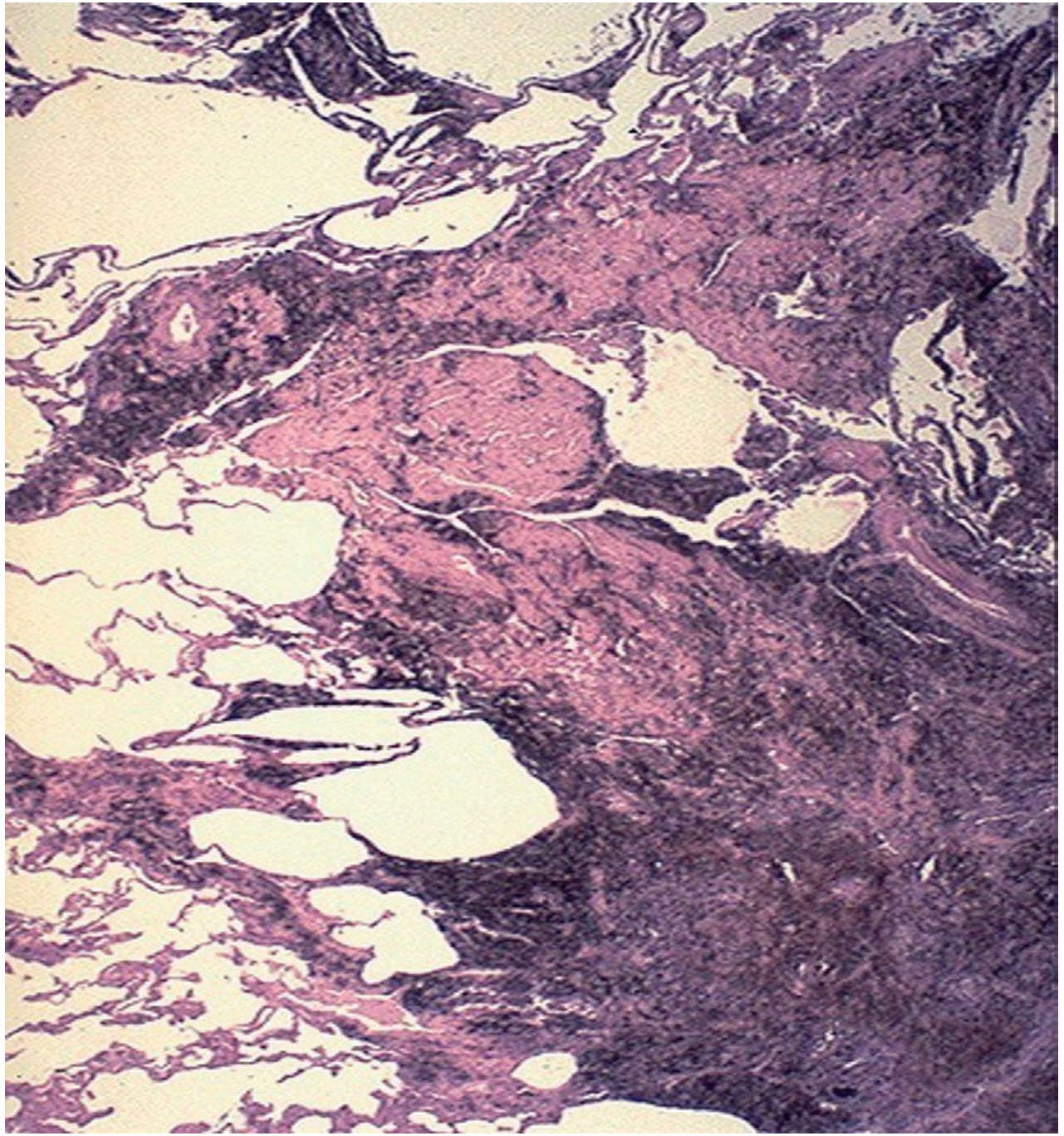
MORPHOLOGY:

Complicated CWP (PMF):

- coalescence of coal nodules that develops over many years

- multiple, dark black scars >2 cm & up to 10 cm consist of dense collagen and pigment

This histologic section shows progressive massive fibrosis with large amounts of black pigment and extensive fibrosis



Klatt EC: Robbins and Cotran atlas of pathology, *ed 2, Elsevier, Philadelphia, p 121.)*

CLINICAL FEATURES

- CWP: benign disease that produces little effect on lung function

- PMF: increasing pulmonary dysfunction, pulmonary ht, and cor pulmonale.

The Progression from CWP to PMF is linked to higher coal dust exposure levels and total dust burden.

- once established PMF has a tendency to progress even in the absence of further exposure.

- No increased risk of lung carcinoma in coal miners. Distinguishes CWP from silica and asbestos **exposures.**

FOR YOUR QUESTIONS:

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Or E-learning

THANK YOU!